

Acquired Haemophilia A: A Case Report.

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CASE REPORT SUMMARY

A 40 year old male patient was admitted in ICU of Hosmat Hospital & Research Centre, Bangalore. There was a history of fall from a motor bicycle. There was a marked swelling over the lower two-third of his right thigh. X-ray of the thigh revealed no fracture. There was a massive muscle hematoma. Hematoma was gradually increasing in size giving indication of persistence of bleeding. The patient also started getting epistaxis. The clinical picture was giving a strong suspicion of a bleeding or coagulation disorder.

Urgent blood samples were sent for CBC with platelet count, PT & APTT, and screening test for coagulation factors. CBC was almost normal with normal platelet count (250,000/cmm). PT was normal with normal INR. APTT was prolonged (> 1 minute). Correction method over APTT revealed presence of clotting inhibitors (autoantibodies) with titre up to 15 BU (Bethesda Units). Screening tests for coagulation factors revealed markedly low activity of factor VIII (about 1%). Other factors were within normal range.

Thus, keeping in view of the above laboratory tests and the clinical picture with no usual precedent personal or family history of bleeding episodes seen in congenital haemophilia, diagnosis of FVIII autoantibody inhibitors or acquired haemophilia A was made. Immediate treatment was required. The main aim was to control the bleeding as well as to eliminate the inhibitor and cure the disease. High dose of Factor VIII concentrate was given in the form of IV infusion. A dose of 200 IU/Kg was given 8 hourly for 4 days and then continued 12 hourly for 6 days more.

From the first day immunosuppressive therapy was also given in the form of IV infusion of Methylprednisolone Sodium Succinate. A dose of 1000 mg was given daily for three days. On the

4th day oral steroid was started in the form of prednisolone (1 mg/Kg). Oral cyclophosphamide was also given (100 mg/day) for 7 days. On the 5th day Factor VIII activity went up to 95% with marked lowering of the inhibitor. It came down to 1 BU. On the 10th day Factor VIII activity was 98% with complete absence of inhibitor. Clinically patient was normal with complete disappearance of the hematoma. Patient was discharged on the 11th day. Oral steroid was continued for 30 days with tapering of the dose. After one month patient was seen in OPD. Clinically he was normal. His blood investigations showed 95% Factor VIII, normal APTT with absence of inhibitor.

(Keywords: acquired haemophilia, diagnosis, coagulation disorder, clotting factors)

DISCUSSION

Acquired haemophilia is a spontaneous autoimmune disorder in which patients with previously normal hemostasis develop autoantibodies against clotting factors, most frequently Factor VIII (48). The development of autoantibodies against Factor VIII leads to deficiency of Factor VIII, which results in insufficient generation of thrombin by Factor IXa and the factor VIIIa complex through the intrinsic pathway of the coagulation cascade.

The development of autoantibodies against Factor IX is less common, and the presence of autoantibodies against factors II, V, VII, X, XI, XIII and von Willebrand is extremely rare (48, 5, 9). Diagnosis of acquired haemophilia can be difficult because of its rarity and because the patient does not have the usual precedent personal or family history of bleeding episodes seen in congenital haemophilia (14). Moreover, the clinical signs and symptoms of acquired haemophilia differ from those of hereditary haemophilia. Its severity at clinical presentation can also make managing

acquired haemophilia challenging. The most common epitopes for autoantibody binding to Factor VIII appear to occur between amino acids 454-509 and 593 in the A2 domain on the heavy chain of Factor VIII, between 1804 and 1819 in the A3 domain on the heavy chain, and between 2181 and 2243 in the C2 domain on the light chain (5, 31, 3). Anti C2 antibodies inhibit the binding of Factor VIII to phospholipids and may also interfere with the binding of Factor VIII to Von Willebrand factor protein, while anti-A2 and anti-A3 antibodies impede the binding of Factor VIII to activated factors X and IX of the intrinsic pathway factor X activation complex (34). It is observed that both alloantibody inhibitors in patients with hereditary haemophilia and autoantibodies in patients with acquired haemophilia appear to recognize the same epitopes on each domain, but the inactivation of factor VIII resulting from these interactions differs (15). Alloantibodies totally inactivate Factor VIII, while with autoantibodies there is an initial rapid inactivation followed by slower inactivation resulting in some level of residual Factor VIII (15, 17).

Acquired haemophilia results from the development of autoantibodies which are mostly of the IgG1 and IgG4 subclasses directed against clotting factors (5, 15, 9). Acquired inhibitors to Factor VIII may be associated with numerous conditions. These include pregnancy, autoimmune disorders (Rheumatoid arthritis, SLE, Multiple Sclerosis, Autoimmune Hemolytic Anemia, Autoimmune Hypothyroidism, Temporal arteritis, Sjogren syndrome, Goodpasture syndrome, Myasthenia gravis, Graves disease etc), inflammatory bowel disease, dermatologic disorders, respiratory diseases, diabetes, acute hepatitis B and hepatitis C infection, and malignancies (both solid tumors and hematologic malignancies) (14, 23, 17, 37, 10).

Rarely Factor VIII autoantibodies arise as idiosyncratic reactions to medications such as penicillin, sulfonamides, phenytoin, methyl dopa, chloramphenicol, interferon alpha, and others (18, 37, 10). It is observed that 50 % of cases of acquired haemophilia A occur in patients who lack relevant concomitant diseases. These cases are idiopathic in nature (14, 22). The present case was also idiopathic in nature as there was no associated disease or history of taking above mentioned drugs.

The clinical picture of acquired haemophilia A differs from that of hereditary haemophilia A. Intra-articular bleeding episodes, which are typical in congenital Haemophilia A complicated by the presence of alloantibodies are unusual in patients with acquired haemophilia A. Instead, hemorrhages into the skin, muscles, or soft tissues and mucous membranes occur in most patients (14). In acquired haemophilia A, bleeding episodes are more frequent and severe in comparison to congenital haemophilia A (10). It is observed that the etiology underlying the difference in bleeding symptomatology between acquired and congenital haemophilia A is unknown (34). Typical signs of acquired haemophilia A include overt bleeding, epistaxis, gastrointestinal and urological bleeding, and retroperitoneal hematomas (14, 34, 9).

Spontaneous bruising and muscle hematomas are most frequent (5). The present case also exhibited a big muscle hematoma over the thigh region. If untreated, bleeding into the muscles may progress into a compartment syndrome, with compression of the neurovascular bundles (34). Subglottic haemorrhage may threaten the airway. Other frequent manifestations of acquired haemophilia A include melena, hematuria, iatrogenic bleeding (particularly following attempts to insert intravenous lines), prolonged postpartum bleeding, excessive bleeding following trauma or surgery and occasionally cerebral haemorrhage may also occur (14, 7).

Due to its frequent confusion with other life-threatening conditions (e.g., DIC) and its occurrence in a typically elderly population, acquired haemophilia A can lead to severe morbidity and even mortality before it is correctly diagnosed (34). Estimates of the mortality associated with acquired haemophilia A range from 7.9% to 22%, with most hemorrhagic deaths occurring within a few weeks of presentation (14). Acquired haemophilia A occurs in all racial groups. Moreover, it has no known genetic inheritance pattern and is seen equally in men and women (34).

It is observed that the vast majority cases occur in older adults. The median age at presentation is between 60 and 67 years (34, 22, 9). The age of the present case at the time of admission was 40 years. It is noted that the age distribution of acquired haemophilia A is typically biphasic. There is a small peak in incidence in women aged

20 – 30 years, and a major peak in males aged 60 – 80 years (14, 9).

Acquired haemophilia A has a worldwide distribution. In the United States, the incidence has been estimated to be 0.2 – 1.0 case per 1 million persons per year. In the United Kingdom, the incidence of acquired haemophilia A has been reported to be 1.48 per million persons per year (10). In India, the incidence of acquired haemophilia A has been reported to be 0.8 – 1.2 per million persons per year (28). However, the above figures may underestimate the true incidence of the disorder given the difficulty in making the diagnosis (14). In addition, some patients with acquired haemophilia A and low titres of inhibitors may not be diagnosed unless they undergo surgery or trauma, which also may lead to an underestimation of the incidence of the disease (14). The incidence of acquired inhibitors to clotting factors other than factor VIII is unknown, although it is significantly lower than that reported with acquired haemophilia A (14). Further, it is observed that there is no known association between an increased susceptibility to develop acquired autoantibodies to coagulation factors and ethnicity (10, 14).

Treatment strategies for acquired haemophilia A have two major objectives – (i) During acute bleeding episodes, effective control of bleeding manifestations is the primary objective. (ii) The ultimate therapeutic goal is to eliminate the inhibitor and cure the disease (14, 34, 19, 23, 10, 22, 11, 12, 40, 30).

Haemostasis is usually achieved by administering infusions of Factor VIII concentrate. The dosing requirements of Factor VIII concentrate are considerably higher in these patients than in those patients with congenital haemophilia (34, 22). The required dose of Factor VIII concentrates can only be predicted roughly from the inhibitor titer. Some clinicians double or triple the dose of Factor VIII that should be given to patients with congenital haemophilia of the same weight (12, 40).

A dose of Factor VIII 200 IU/Kg IV bolus every 8-12 hours has been recommended (30). The same dose was given to the present case and it showed excellent result. Patients with very low titer inhibitors (less than 3 BU) and residual Factor VIII activity may also benefit from treatment with desmopressin. IV infusion of desmopressin (0.3 mcg/Kg) may result in a 2 to 3 fold temporary

increase in Factor VIII and von Willebrand factor plasma levels (12). However, in most patients with acquired factor VIII inhibitors, desmopressin treatment will not provide hemostasis (34). Sometimes, when the inhibitor titer is high (more than 5 BU), Factor VIII concentrates and desmopressin are ineffective (15, 19). Such cases should receive therapy with an agent that bypasses Factor VIII, either with recombinant factor VIIa (rFVIIa) (25, 34, 30, 12, 24, 4, 20, 38) or with an activated prothrombin complex concentrate (APCC) (34, 24, 30, 41, 11, 22, 5).

Recommended dose for rFVIIa is 90-120mg/Kg every 2-3 hours IV bolus until bleeding is stopped (34). If no response after two doses, 120-270mg/Kg every 2-3 hours IV bolus should be administered (30). The recommended dose for APCC is 50-100 IU/Kg every 8-12 hours IV bolus (30). Doses should not exceed 200 U/Kg within a 24 hour period (34). Patients who do not respond to rFVIIa or APCC can either receive combined rFVIIa and APCC or immune-adsorption/plasmapheresis (30).

Extracorporeal removal of the autoantibody can be accomplished using therapeutic plasmapheresis or specific immunoadsorption of immunoglobulins (14, 16, 45, 26, 21, 39). Immunoadsorption may be particularly useful when a rapid reduction in the titer of inhibitor is required (11). Following plasmapheresis or immunoadsorption, Factor VIII replacement should be initiated to achieve hemostasis (34).

Eradication of the inhibitor is an important step in the treatment of acquired haemophilia A. It should be attempted using immunosuppression as soon as the diagnosis of acquired haemophilia A is made (23). Eradication of inhibitor is essential to restore normal hemostasis and minimize the patient's risk of bleeding (23). After eradication of inhibitor, patients who achieve complete remission have been shown to have a better outcome in terms of overall survival (12). However, it is observed that in patients with mild haemorrhagic symptoms and low levels of inhibitors, immunosuppressive therapy may not be required and about 25 % of patients may achieve spontaneous remission without immunosuppression (33). According to majority of clinicians, as the patients remain at risk of fatal bleeding until the inhibitor is completely eradicated, all patients should be immunosuppressed as soon as the diagnosis is made (10).

First line of therapy for eradicating inhibitors includes methylprednisolone or prednisolone at a dose of 1 mg/kg/d, which results in the abolition of inhibitors in about 60-70% of patients (23, 12). In the present case, as the titer of inhibitor was high, methylprednisolone sodium succinate was given IV with a dose of 30 mg/Kg/d for 3 days followed by oral dose of prednisolone (1 mg/Kg). This resulted in complete disappearance of inhibitor. Adding oral cyclophosphamide 50-150 mg/d can increase the response rate to 70-80% (23, 12). In the present case cyclophosphamide was also given.

Other cytotoxic agents that have been used include azathioprine, vincristine, mycophenolate mofetil, 2-chlorodeoxyadenosine (34, 18, 32, 13, 42). Rituximab, an anti-CD20 monoclonal antibody, has shown promising results in eradicating inhibitors in acquired haemophilia A (34, 27, 49, 1, 36). The usual dose is 375 mg/m² each week for 4 weeks. Cyclosporine has been used as salvage therapy alone or with prednisolone and it is particularly effective in patients with underlying SLE (34). Infusion of intravenous immunoglobulin (IVIG) may be useful as a second line therapy for patients who do not initially respond to immunosuppression (34, 10, 23).

Recent immune tolerance induction regimens involving immunosuppression and immunoabsorption (e.g., the modified Bonn-Malmö protocol (MBMP)) also have been shown to rapidly eradicate autoantibody inhibitors (30, 50). This protocol includes a combination of cyclophosphamide, prednisolone, large volume immunoabsorption, intravenous immunoglobulin, and Factor VIII (50).

Sometimes in acquired haemophilia A with life-threatening bleeding episodes, surgical management may be required (44). Techniques that may help stop these haemorrhages are classified as mechanical (ligature placement or selective embolization), thermal (electrocautery or cryotherapy), and chemical (chemical agents with hygroscopic properties or acting as micronized collagen) (44).

It is observed that patients with acquired haemophilia A can bleed spontaneously or after negligible or minor trauma. Any physical activity may trigger bleeding in soft tissues. Until inhibitors are eradicated completely, patients with acquired haemophilia A should avoid activities

with a significant risk of trauma. The present case developed massive hematoma of the thigh after trauma.

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